Potential Reduction in Incidence and Mortality Simulation Transcript

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DR. YABROFF: Good morning, again. And I would like to reiterate again how disappointed my colleague, Jeanne Mandleblatt, was that she was not able to be here to participate in this process. But basically what we did, as Jon mentioned, as part of our review, was to use an existing cervical cancer, natural history of disease model, to look at some of the pathways that we've been discussing about reducing cervical cancer mortality. So what is the impact if you reduce HPV prevalence, for example What is the impact if you increase screening rates What is the impact if you improve treatment To help us try and understand where you can help think or start thinking about where to invest your limited resources in terms of improving cervical cancer mortality.

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Before I start, I am just going to do a very quick review of some of the things that we talked about yesterday. What do we know about cervical cancer incidence We see that factors associated with high rates of risk factor prevalence are concentrated in rural areas, although we really have very little data on what those prevalence rates actually are. We don't know what the prevalence rate of HPV is in different geographic regions. We have a good idea of what it is nationally, but really not much idea of what's going on in different regions of the county -- smoking, sexual practices, micro-nutrients, we just really don't know very much. But there are some things we would like to know and this is some of the things we're hoping to do with our simulation model. Is risk factor acceptable Is it cost- effective Is it effective What happens if you do commit to risk factor reduction Will things like HPV testing or other technologies improve outcomes There are a lot of other -- we've heard things about thin-prep, about HPV vaccinations, but really, what really would the impact be of those things How widely would we expect them to be used

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Screening, follow-up, and stage of disease of diagnosis. We do know, again, that population characteristics that are associated with low rates of screening, low rates of follow up and high rates of late stage and disease and diagnosis are concentrated in rural areas. However, when we look at national data or when we look at region specific

data, we don't see big differences in screening rates. We don't see big differences in follow-up rates and we have very little data to know whether or not stage of disease at diagnosis -- those distributions are different than what they are nationally. However, again, as we do know, when you take women that have been diagnosed with invasive disease, and you back track what happened along the pathway, most of them did not receive Pap smear screening or they haven't received it recently. So we know that it's a problem, indicating there might be pockets of women that are underscreened that we're not identifying with large surveys. There are a lot of things that we do need to know in order to determine what's going on. What are the rates of follow-up Are they low And if so, what types of interventions can we use to improve follow-up rates What's going on with regular screening And again, what can we do to improve rates of regular screening To women who fail to follow-up, do they ever return Or do they just fall out of the system, never to receive another Pap smear, only to surface 15, 20 years later with invasive disease. We really need to know some of those things. And also important to you, in terms of making decisions about what you want to implement in your communities. What are the most cost-effective interventions in terms of reducing risk factor prevalence, increasing screening and follow- up, and improving treatment

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In terms of treatment we do know that most women do get some form of treatment, but we really have very little information on patterns of care. What are treatment patterns by hospital Presence or absence of hospitals Provider characteristics or patient characteristics Not only are they getting care, but what is the quality of the care they are receiving We have very little information on that. However, at the same time, we need to move forward -- and so that is the main reason that we decided to use a simulation model. So, in the absence of data, or at least data that tell you what's going on in your specific area, we used large national -- where possible nationally representative data to build a simulation model. This model was originally developed to look at the cost- effectiveness of HPV in combination with Pap smear. A series of different combinations. And we adapted it specifically to try and address some of the questions we thought that you might need addressed, but also things that you might be curious about. What is the impact of some of these strategies

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The simulation model itself, as I said, already exists. It was a model to

look at HPV and HPV screening and Pap smear screening and it addressed a lot of things that have come up, although we probably won't be getting into that today. Things like, what is the best upper age limit to stop screening When should you start screening What is the best periodicity The model does address some of those things, although again, I'm not really going to get into that in great detail. The model was validated against several existing sources, including inputting HPV prevalence data in an unscreened population and predicting incidence of invasive disease. And it's very well validated. It's comparable to other simulation models that people have done to look at cervical cancer incidence. The model uses its 17 health states -- so there are different women progress through the model. They start at, I think it's age 20, and progress through from healthy to LSIL, HSIL, invasive disease, and then through death. And the transition probabilities are based on published data, studies that have been done to look at how women move through the process. And overlying that model will be the different cervical cancer control interventions that we've been talking about. There are some key assumptions. This model, obviously is based on what we know, and unfortunately, we don't have perfect information. But we did assume that HPV infection is the key event. That 95 of invasive cervical cancers develop from HPV. There is a sub-model that looks at cases that develop outside of HPV, but we are making assumptions based on the role of HPV. We assume that the baseline screening rate was 78 . Although this is age specific -- we have lower screening prevalence in older women, higher screening prevalence in younger women. We also assumed a 100 percent compliance with testing every three years. And we looked at triennial screening throughout lifetimes. So starting at age 20, every three years, all the way up until death. We also assumed 100 compliance with follow-up and treatment.

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So for some preliminary results, and I'll show you a table in a minute, where we can actually go through numbers, but this is just a summary. Reducing HPV infection by half of the current rates would reduce incidence and mortality by about 42 from current levels. So, if you are in a community where you think that the main force driving is not screening and it's not treatment, it's that you have a really high prevalence of HPV infection, this might be a strategy that you might want to thing about. Additional screening could save lives if screening rates are currently below 60 percent and they're increased above 75 percent. So if you live in a community where you think that you have underscreened pockets of women, who have just never, ever been

screened, increasing screening in your community may be an important mechanism to decrease mortality. Test sensitivity. If you can increase test sensitivity, maybe through one of the newer technologies. If you can increase it to above 70 percent, you're also going to reduce mortality. Finally, if you use low-sensitivity tests, such as the Pap smear more frequently you will reduce mortality, although there will be more false positives and other constraints on the infrastructure of your health system. Finally, adding chemotherapy to invasive treatment, while very effective in improving survival, only has modest gains in terms of reducing mortality.

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Can everyone see these numbers This table basically describes the number of incident cases that would be averted if any of these cancer control interventions were implemented in the first column. And in the next column is the number of deaths that would be averted if these interventions were implemented. So the first possible intervention is reducing HPV prevalence to half current rates. If we do that, 323 cases of cervical cancer would be averted. That's a 42 percent reduction. And 114 deaths would be averted. And in the next potential set of interventions, this is improving compliance with triennial screening. So increasing the numbers of women that are getting screening every three years: if that number is increased from 40 to 78 , 848 cases would be averted for a 53 percent reduction in cervical cancer incidence. That also would lead to 439 deaths averted and 63 reduction in deaths. Increasing compliance with screening from 78 to 90 percent, however, is associated with a much lower impact on incidence, as you might expect. At some point, you do hit that asymptote. One hundred and eighty-nine (189) cases would be averted, and that's a 25 percent reduction in cervical cancer cases. That's also associated with 89 cancers deaths averted for a 34 percent reduction in deaths. The next strategy we evaluated was decreasing the interval between tests from three to two years. So, again, this would be women being screened every two years from age 20 until death. This would avert 317 cases of cervical cancer for a 41 percent reduction. And 131 deaths for a 49 percent reduction. But again, increasing screening periodicity with a test with low sensitivity is also going to put further constraints on your health-care system. Finally, and I hope I didn't oversell yesterday, I mentioned that we might be talking about new technologies. But what we really tried to focus on is what would be the impact of a new screening technology, rather than the technology itself. So increasing the sensitivity of a Pap smear or introducing a new test with improved sensitivity, from 70 to 90 ,

would also be associated with reduction in cases -- 303 for a 39 percent reduction and a 48 percent reduction in deaths. So that's also potentially, a very effective mechanism for reducing cervical cancer mortality. Finally, adding chemotherapy to existing treatment regimens, which doesn't have an impact on incident cases, but it does reduce deaths by approximately 30 percent.

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So based on the model findings, you would conclude that you would want to invest in HPV prevention. That's very effective in terms of reducing both cases and deaths. If you have pockets in your communities where you think there are women that are just not getting screened at all --- improving rates with screening in those communities would also be very effective in terms of reducing both incident cases and deaths. Improving the quality of Pap smears, screening more often, or a better screening test would also, not surprisingly, reduce the number of cases and the number of deaths. And finally, while screening more frequently with the poorer quality test is not likely to be cost-effective, because it is going to add additional constraints in terms of false positives and treatment of women who have disease that is likely to regress. So that is all that I had prepared. I would like to mention that while I did participate in trying to think about how to use the existing model to give information that might be useful for you all, the underlying natural history disease model is not something that I was heavily involved in. So, if you do have questions about that, I'll be happy to try and answer, but I may not be able to answer right now, and I may have to refer you to someone else to answer at a later date. So if we can mostly focus on the simulations that we used here, rather than the underlying model, I'll be happy to answer any questions.

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DR. KERNER: As usual, Robin has got us back on time again because she delivers a lot of information in a really short amount of time, and I'm very grateful for that. So we have some time for questions if you want to knock up the lights there for a minute. Are there any questions about -- and my goodness, there's a question from Joe Harford, from the NCI. Yes, Joe -- would you introduce yourself JOE HARFORD: Hi Robin. Good to see you again. I was just confused a little bit about the table on cases averted and deaths averted in terms of what timeframe. Is this over the whole life of the woman from 20 years on DR. YABROFF: Yes. We don't know what age that case would occur. DR. HARFORD: So you're saying, that if we screen a woman

every three years for her whole life, that we will see an advantage of dropping that to every two years, and every year, even though we would have presumably caught the woman who has a positive Pap test at age 22 -- is going to get caught somewhere along the line, irrespective of the frequency, if she has a whole lifetime of screening. DR. YABROFF: Right. DR. HARFORD: I'm just trying to understand what those numbers in terms of cases and deaths averted mean over lifetime. DR. YABROFF: Okay. The screening tests are not perfect even though women would be continuing to get them. We were going to assume that are going to be new cases of HPV infection over a woman's lifetime. So even though at 22, she may not get caught, she may not have an HPV infection at that point, it may not occur until 40 or 50 or -- . DR. HARFORD: This is a Pap test, not an HPV DR. YABROFF: I understand. I understand, but women are developing cervical cancer over time as well as getting tested over time. I'm not sure that answers your question. DR. HARFORD: Well, I mean, we're going back to the natural history of disease that's 30 years and progressing. It just struck me that these seem to be fairly dramatic changes in cancer incidence. Cases caught and deaths averted, for dropping from three to two years. Then the other related question -- you said you assumed 100 compliance with that, and you assumed 100 follow-up. And we've obviously heard that we don't have 100 compliance with either of those two things. Did you try in the modeling to introduce changes in that compliance assumption DR. YABROFF: No. DR. HARFORD: To see whether or not if you only got 90 follow-up, what impact that would have DR. KERNER: Could we do that DR. YABROFF: Yes. DR. KERNER: Okay. That's good. I think it's important to recognize that in a simulation model, the assumptions often drive the magnitude of the effects, to some extent. DR. YABROFF: Yes. DR. KERNER: And so you're raising questions about how we might alter those assumptions to look at that. That's a good point. The other thing to say is that the relative differences may be more important than the absolute differences because it is a simulation model. And then I would focus on Robin's last point, which is while there may be some -- . You'll look at this and say, well, gee, "why aren't we just screening more frequently." Remember her last bullet point -- that the cost- effectiveness of frequent screening, particularly in settings with limited resources, may make the sort of perceived benefit, you're not really taking into account the enormous impact that's going to have on a very strained health-care system. And as Nancy Lee pointed out last night, at that level there are trade-offs when you start doing a lot more activity in one area, what are you

going to have to give up somewhere else So I do think that that's an important part of the puzzle. DR. YABROFF: Let me just reiterate that we did not include costs here, but again, when you do include costs of things like decreasing frequency from three to two years The costs are off the chart. It's very expensive. DR. KERNER: George, my favorite. DR. SAWAYA: I'm at the microphone mainly to defend the Pap smear. There's this general -- . I know where it came from. But there is this general thought -- . DR. KERNER: Are you going to tell us DR. SAWAYA: Yes. But I won't be too explicit. But there is a general thought that the Pap is a bad test. It's a poorly accurate test. And I want to be just clear that the Pap is an excellent test. It's not only been so excellent in the way we've applied it, but it's also translated into really great, profound decreases in incidence and mortality of cervical cancer. Now, although the Pap smear has some -- . I also want to be clear that we do not know with very good precision what the true accuracy of any of the tests that we screen with actually is, including the Pap smear, including liquid- based cytology, including HPV testing. And if you try to look in the literature, and believe me, I have, and I've published meta-analyses and systematic reviews on this particular topic, you're astounded by the lack of data by what these numbers actually are. One number that keeps coming up is this 51 sensitivity for the Pap smear, and that number is based on if a woman has a low-grade biopsy and a negative Pap smear -- that she is just as bad in terms of a false negative as a woman who has CIS and a negative Pap smear. And I think that is a fallacy. So I think we have to be very careful about talking about the relative differences in sensitivity between different screening methods, when in fact we're operating in the dark, by and large. And even though we may be able to increase the sensitivity of the test, one of the great bonuses of the Pap smear is that it probably has a fairly superior specificity. And we can always increase the sensitivity of the test. I can make up a test that is 100 sensitive because it's positive all of the time, but it may have absolutely no specificity. So we have to be very clear that although we have some incremental increases in sensitivity that who loses out in the game may be women who are dragged along by false positive testing due to less specific tests. And that's also a big unknown for the newer ways with which people are promulgating that women be screened. DR. YABROFF: Right. Thank you. And one of the reasons that we restricted this to Pap and instead of using one of the newer technologies is because there is very little data out there. But I also would like to say that the sensitivity and specificity values we used were based on HSIL and above. So those values are actually much

better than when you start looking at LSIL . DR. SAWAYA: The other point to make is that if you make assumptions about the specificity in that they do not change, then that's probably a false assumption. DR. YABROFF: Age specific. DR. SAWAYA: Did you change the specificity to go down with an increase in sensitivity or did you keep the specificity the same DR. YABROFF: The specificity changed and also the sensitivity and specificity are age- specific. DR. SAWAYA: And so when your sensitivity went up for a new screening test, did your specificity go down concurrently DR. YABROFF: Yes they were. They were not considered to be independent -- is what your saying DR. SAWAYA: Right. Because that issue of specificity drives cost. DR. YABROFF: Oh definitely. And that is a big point. And I think we should make it again. That if you do increase screening frequency, you are going to increase false positives and again, drag women along throughout the treatment process. DR. KERNER: Okay, great. Next. MS. FISHER: I'm Shannon Fisher. In your conclusion you stated that the screening, more often with poor quality tests. So is that poor quality test technique, or is that specific to testing method: thin-prep versus the slide method. DR. KERNER: Poor choice of words. DR. YABROFF: Poor choice of words, I think, is the best -- . DR. KERNER: Which I think wa